Remarks

Claims 1-9, 11-16, and 18-19 are pending. Claims 1, 8 and 14 have been amended to more clearly define the claimed invention. Claim 18 has been cancelled as duplicative. Claims 20 and 21 have been added, for which support can be found throughout the specification, and particularly at pages 17-18, and 20. A copy of the claims as amended is enclosed in the attached Appendix for the Examiner's convenience.

Drawings

Formal drawings will be submitted when there is allowable subject matter. The application was filed with informal drawings.

Trademarks

The specification has been amended to capitalize trademarks and insert the generic terminology to the extent known.

35 U.S.C. § 101

The withdrawal of the rejections under 35 U.S.C. § 101 is appreciated.

Rejections under 35 U.S.C. § 112, First Paragraph

The specification has been objected to and Claims 1-9 and 11-16 have been rejected under 35 U.S.C. § 112, first paragraph, for failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention. These objections and rejections are respectfully traversed.

The basis for the rejection appears to be the unsupported allegations of the Examiner that the method would require undue experimentation and that pigs are not predictive of efficacy in humans. These arguments fail in view of the accompanying evidence, attached as Exhibits A and B.

A. Enablement

The requirement under 35 U.S.C. §112 is that applicant must provide a written description of how to make and use the claimed invention, i.e., a method of inhibiting microvascular bleeding such as exists at the surface of a burn wound, and a composition for administration to a patient of an inhibitor of a natural anticoagulant in combination with a topical coagulant. These two embodiments of the disclosed invention will be dealt with separately.

The composition

§112 requires that the composition must be enabled by the specification for at least one alleged use. There is no requirement that each embodiment be actually reduced to practice.

Pages 6-14 provide a clear description of those inhibitors defined by the independent claims and inhibitors thereof; page 13 describes the topical coagulants that are available.

Pharmaceutically acceptable carriers are described at page 14, lines17-20.

The effective dosage of inhibitor of an anticoagulant is described at page 14, lines 21-27, and page 15, line 29 to page 16, line 24. The effective dosage of the topical coagulant is described at page 16, lines 25-31.

Topical coagulants and effective dosages are also well known to those skilled in the art; see, for example, Furie, et al., Cell 53, 505-518 (1988); Suzuki, et al., Thrombosis Res. 53, 271-277 (1989); and U.S. Patent No. 5,130,244, copies of which are enclosed.

The example at pages 17 to 21 demonstrates reduction to practice and efficacy of the claimed composition.

The method of treatment

The methods and examples described in the application are enabling and predictive of treatment in humans.

Pages 13 to 14 describe the disorders which can be treated. The example at pages 17 to 21 demonstrates actual reduction to practice.

As noted above, the compositions and effective dosages are clearly defined in the application. Although the Examiner seems to be concerned regarding the possibility of pathologic thrombosis whenever a systemic thrombogenic drug is utilized, no evidence has been provided that one would expect such a condition to occur. Applicant is an M.D. who is actively treating patients, as well as a researcher. The consideration of pathologic thrombosis stems from abnormalities associated with congenital deficiencies in protein C, not from the transient inhibition of protein C, as described at page 14, last paragraph. The

Examiner's attention is again directed to page 15, wherein lines 29-33 state that titration of the dosage is possible so that inactivation of a specific fraction of the circulating protein C pool is achieved. Dosage titration is well known in the art, and can be applied to achieve the desired results. Also, on page 16, lines 12-16, describes how normal protein C activity can be reestablished by administering extrinsic "pre"-activated protein C. One skilled in the art could apply one of these procedures for use in conjunction with use of any of the claimed agents if so desired.

B. Safety and Efficacy

First, U.S. Patent No. 5,147,638 to Esmon, et al. describes the intravenous administration of the same anti-protein C antibody used in the examples (HPC4) to treat solid tumors in **dogs and pigs** (examples in the patent) and in **cats and primates** (prosecution history), not only with no detrimental side effects, but with tumor reduction, providing conclusive evidence that the protein C pathway is blocked. Other antibodies and inhibitors are also described for use in inhibiting the protein C natural anticoagulant pathway and evidence of efficacy was submitted during prosecution of the patent, leading to the broad scope of the issued claims.

See also U.S. Patent No. 5,202,253 to Esmon, et al., at col. 2, lines 62-66 (HPC4 binds to the activation region of human, pig, baboon, and canine protein C).

Second, as described in Genetic Engineering News, October 1, 1994, and the University Hospital Consortium, UHC Biotechnology Monitor, January 1994, many

antibodies are being developed for use in clinical treatments, including the Centoxin antibody of Centocor, although for a more specific indication. The antibody was not at fault in this case; the diffuse and uncharacterized nature of sepsis provided erratic results. Many non-human antibodies are either in phase III or approved for use in humans, either therapeutically or diagnostically. See, for example, the brochure on "ONCOSCINT CR/OV", "DIGIBIND" Digoxin Immune FAB (ovine), NeoRX product brochure, and articles by Petersen, et al., Amer. J. Surg. 165, 137-143 (January 1993), Markowitz, et al., Clin. Nuclear Med. 18(8), 685-700 (1993).

In response to the question as to why and how the print out listing 1308 titles submitted by Applicant establishes that murine antibodies can be used for the treatment of human disease, one purpose of submitting the print out listing the titles of more than 1,000 1991 and 1992 publications having the terms "monoclonal antibody" and "therapy" therein was to show the continued overwhelming scientific interest in the area, and to show generally how much research is done per year since Waldmann's 1991 statements.

Third, the articles cited by the Examiner in support of his position are irrelevant to the issues in this application, which deals with whether or not applicants has provided a written description enabling one of ordinary skill in the art to make and use the claimed invention without undue experimentation and if the example using pig is predictive of efficacy in humans. It should be noted that those skilled in the art of **treating humans** think

the technique to be useful, as judged by publication in the Journal of Surgical Research (1992), a journal not inclined towards treatments directed solely at pigs.

Moreover, and perhaps more importantly, the pig is not used as a predictor of efficacy of treatment of **skin, but of the coagulation system and microvasculature**. The Examiner has provided no evidence that the coagulation system of the pig is not predictive of the coagulation system and microvasculature of humans and in fact the Esmon patent is conclusive evidence of the predictability and cross-species homology in this respect.

With respect to Montagna, et al., this is merely a review article that says that there are differences in pig and human skin. Again, it is the **physiology**, not the histology that is relevant: pig has a microvasculature similar to that of humans (Montagna, et al.) and a clotting cascade that results in clotting following administration of HPC4 in pig tumors (see Esmon, et al.); therefore it is predictive of efficacy in humans and other animals.

With respect to the statement in the specification regarding further study prior to widespread clinical use at lines 26-30 of page 21, Applicant respectfully submits that this statement was made in consideration of certain regulations and out of an abundance of precaution not pertinent to the requirements of patentability. In fact, lines 9-13 of page 21 state that this study demonstrates that the transient blockade of protein C activation provides a new systemic alternative to topical hemostatic measures that is safe and equally as effective as topical thrombin or tissue thromboplastin at their standard commercially available

concentrations; and, lines 20-21 of page 21 state that these results can be applied to the clinical setting of grafting extensively burned patients.

With respect to Waldmann, this is merely a review of the advances in monoclonal antibody-mediated therapy which enhance already effective therapy. The statements quoted by the Examiner do not teach that success in humans cannot be predicted from success in animal models, but merely state that it is desirable to further enhance the effectiveness in humans. In point of fact, Waldmann offers an explanation of the lower therapeutic efficacy in humans. Specifically, Waldmann states that *in most cases*, the antibodies that were not efficacious were not directed against a vital cell-surface structure such as a receptor for a growth factor required for tumor cell proliferation, page 1657, second column, first paragraph (emphasis added). In the present invention, the targeted substrates are primarily circulating in the plasma; and therefore, Waldmann's solution to the problem found in most cases is inapplicable to the present invention.

Harris et al. summarize two conferences on the progress of obtaining effective mAbs for therapy, noting three problems with the use of rodent mAbs and that four approaches to overcoming these deficiencies formed the basis of the conferences. Applicant respectfully points out that Harris et al. supported the statement above regarding the future of rodent mAbs for *in vivo* human therapy, by noting the absence of new clinical data presented at this annual event, page 42, column two. Applicant submits that certain regulations surrounding obtaining clinical results, not pertinent to patentability requirements, make this process

extraordinarily time consuming and difficult; and therefore, the lack of new clinical data from one year to the next is not indicative of what one skilled in the art considers a viable therapeutic approach. Also, a number of factors unrelated to therapeutic effectiveness may determine whether a certain therapy has a "future", and therefore, this statement is not indicative of what one skilled in the art considers effective.

With respect to half-life, this again goes to the issue of clinical efficacy; not enablement. The requirements are distinct and what may be required for commercial success is not required for enablement under §112.

Regarding the legal standard of the predictiveness and relevance of animal models, the Examiner's attention is drawn to *Engelhardt v. Judd*, 369 F.2d 408 (1966), wherein the United States Court of Customs and Patent Appeals held that an inventor's reference to dosing humans in his specification does not preclude him from proving actual reduction to practice of a drug by successful utility testing on standard experimental animals. Specifically, on pages 410-11, Section 3, the Court relied on the record's satisfactory evidence of the correlation between antihistamine and antiserotonin activity in laboratory animals and in human beings. More specifically, to find the correlation, the Court relied on expert testimony affirming the following two questions: 1) Did you know whether the tests were related to activity in humans?; and 2) Were you able to expect this activity in man from the activity in animals? In fact, the answered testimony to the latter question was "We would have predicted it, so it would have been surprising had it not occurred." Therefore,

given the successful animal model results disclosed in the present application, and the known anticoagulant activity of protein C and the other cited anticoagulants in humans, (see page 6 last paragraph), Applicant has met his burden of proof that the claims are enabled.

35 U.S.C. § 112, First and Second Paragraphs

Claims 14-16 were rejected under 35 U.S.C. § 112, first and second paragraphs, as indefinite. This rejection is respectfully traversed if applied to the amended claims.

Claim 14 has been amended to clarify that the composition consists of two components, an inhibitor of a natural anticoagulant and a topically administered coagulant.

With respect to the term "block", this has been replaced with the phrase that the amount is effective to prevent anticoagulation by the protein C.

Claim 18 has been cancelled, as noted above

Rejections under 35 U.S.C. §103

Claims 1-3, 7, and 11-13 were rejected under 35 U.S.C. § 103 as obvious over U.S. Patent No. 5,202,253 to Esmon et al. Claims 4 and 18 were rejected under §103 as obvious over Esmon et al., in combination with U.S. Patent No. 5,130,244 to Nishimaki, et al. Claims 5, 6, 8, 9, 14-16, and 19 were rejected under §103 as obvious over Esmon, et al, in combination with Nishimaki, et al., and Furie, et al., Cell 53, 505-518 (1988). These rejections are respectfully traversed.

Esmon, et al.

Esmon, et al., is drawn to a particular, very unique antibody due to the requirement of calcium for binding. This makes the antibody particularly useful for purification, since bound protein can be easily eluted using a calcium chelator. **In patients having high levels of factor VIII inhibitors** (that is, hemophiliacs whose blood does not normally clot), the antibody can be used to promote normal clotting. However, presumably these are people who are not in need of microvascular clotting; they are people whose blood does not clot normally. Therefore, the claims in the present application are not obvious; there is simply no motivation from a disclosure suggesting **normalizing of clotting in a hemophiliac** to treatment of people suffering from microvascular bleeding, but who otherwise clot normally. Esmon et al. teaches that the antibody can be used to promote clotting in patients having clotting factor deficiencies, as described at column 13, lines 17-22.

U.S. Patent No. 5,130,244 to Nishimaki et al.

Nishimaki, et al., merely discloses a sugar stabilized aqueous thrombin preparation. There is nothing regarding using the topically applied preparation in combination with anything else, much less a systemically administered anti- natural anticoagulant.

Furie, et al.

Furie et al. reviews the coagulation cascade. There is nothing regarding combining a topically applied coagulant preparation in combination with anything else, much less a systemically administered anti- natural anticoagulant. In fact, the authors conclude with the

statement regarding the complexity of the clotting system and the interaction of soluble components with cell bound components.

The requirement under §103 is that the prior art must disclose each claimed element as well as provide the motivation to combine as applicant has done, with the expectation of achieving the desired result. There is simply no such motivation in the cited art.

Allowance of claims 1-17 and 19-21, as amended, is earnestly solicited.

Respectfully submitted,

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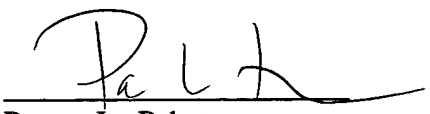
CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)

I hereby certify that this Amendment, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: August 17, 1995



Patrea L. Pabst

APPENDIX: *Claims as Amended*

1. (three times amended) A method for inhibiting microvascular bleeding at a site in a patient exhibiting microvascular bleeding comprising administering to the patient a compound in a pharmaceutically acceptable carrier in an effective amount to prevent anticoagulation by greater than 90% of activated protein C in human plasma, wherein the compound is an inhibitor of an anticoagulant selected from the group consisting of protein C, antithrombin III, heparin cofactor II, thrombomodulin and tissue factor pathway inhibitor.

2. (amended) The method of claim 1 wherein the anticoagulant is protein C.

3. The method of claim 1 wherein the inhibitor is administered systemically.

4. The method of claim 1 wherein the inhibitor is administered topically.

5. (amended) The method of claim 1 further comprising topically administering at the site of the bleeding a coagulant.

6. The method of claim 5 wherein the coagulant is selected from the group consisting of thrombin and tissue thromboplastin.

7. (amended) The method of claim 2 wherein the inhibitor is an antibody to protein C.

8. (twice amended) The method of claim 7 wherein the inhibitor is administered systemically further comprising the step of topically administering a coagulant at the site of bleeding.

9. The method of claim 8 wherein the topically administered coagulant is selected from the group consisting of thrombin in a dosage of between approximately 1000 and 10,000 units and tissue factor in a dosage of between approximately 0.1 and 10 mg.

11. (amended) The method of claim 1 wherein the inhibitor is administered to a burn patient.

12. (amended) The method of claim 1 wherein the inhibitor is administered to a patient with tissue or skin grafts.

13. (amended) The method of claim 1 wherein the inhibitor is administered to a patient with cerebral contusions.

14. (Three times amended) A composition for inhibition of microvascular bleeding comprising as a first component an inhibitor of a natural anticoagulant selected from the group consisting of protein C, thrombomodulin, antithrombin III, heparin cofactor II and tissue factor pathway inhibitor in a pharmaceutically acceptable carrier for systemic administration to a patient and as a second component a coagulant in a pharmaceutically acceptable carrier for topical administration to a patient.

15. The composition of claim 14 wherein the inhibitor specifically inhibits protein C.

16. The composition of claim 14 wherein the coagulant is selected from the group consisting of thrombin and tissue thromboplastin.

19. (amended) The method of claim 18 further comprising the step of [topical administration of] topically administering a coagulant at the site of bleeding.

20. The method of claim 3 wherein the inhibitor is a monoclonal antibody immunoreactive with protein C and blocking protein C activation.

21. The method of claim 20 wherein the inhibitor is HPC-4, deposited with the American Type Culture Collection, Rockville, MD and assigned ATCC No. 9892.